Attorney Docket No.
PC10408A

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By _____
(Signature of person mailing)
Jason G. Tebbutt

(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: Susan B. Sobolov-Jaynes

APPLICATION NO.: 09/707,320

FILING DATE: November 7, 2000

TITLE: COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY

Examiner: Jarvis, W.

Group Art Unit: 1614

Commissioner for Patents
PO Box 1450
Arlington, VA 22313-1450

Sir:

RESPONSE TO NON-COMPLIANT APPEAL BRIEF (37 CFR 41.37)

In response to the Notice of Non-Compliant Appeal Brief (37 C.F.R. § 41.37) mailed November 9, 2005, appellants submit herewith an amended Appeal Brief originally filed on October 6, 2005. The Appeal Brief has addressed all of the points made by the Examiner in the Notice of Non-compliant Appeal Brief. With regard to Examiner's point 4, the "Summary Of Claimed Subject Matter" now refers by page and line number to each independent claim. With regard to point 6, after a telephonic conversation with Kimberly Jordon at the USPTO, it was

agreed that this objection was in error. With regard to point 8 and 10, an "Evidence Appendix" and "Related Proceedings Appendix" have been added.

Accordingly, this appeal brief now complies with 37 C.F.R. § 41.37. A shortened statutory period for response to the November 9, 2005 Notice is set to expire one (1) month from the mailing date of the Notice, i.e., December 9, 2005. Accordingly, this response is timely filed. If any additional fee is due, the Examiner is authorized to charge the fee to Applicants' Deposit Account No. 16-1445.

STATEMENT OF THE CASE

This is an appeal from the Final Rejection of September 24, 2002, finally rejecting claims 1-16 in the above identified application, under 35 USC 103(a), as being unpatentable over U.S. Patent 5,773,450 (Lowe, III et al) in view of The Merk Index List. Claims 1-16 also stand rejected provisionally under the doctrine of obviousness-type double-patenting as allegedly unpatentable over claims 1-35 of copending application 09/867,079 and claims 1-33 of copending application 09/867,357.

A petition for a 2-month extension of time is filed concurrently herewith. Accordingly, this appeal brief is timely.

REAL PARTY IN INTEREST

The real party in interest in the present appeal is Pfizer Inc. of 235 East 42nd Street, New York, New York 10017, assignee of record.

RELATED APPEALS AND INTERFERENCES

There are no related appeals, or interferences which would have any affect or which would be affected by or have a bearing on any decision in the present appeal.

STATUS OF THE CLAIMS

Claims 1-16 are the subject of the present appeal and in the appendix herewith.

STATUS OF THE AMENDMENTS

No amendments have been made in response to the Final Rejection of September 24, 2002.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a method of treating depression or anxiety in a mammal, including a human, by administering to the mammal a CNS-penetrant NK-1 receptor antagonist (e.g., a substance P receptor antagonist) in combination with an antidepressant or an anxiolytic agent. (see specification; pages 2, lines 13-18). It also relates to pharmaceutical compositions containing a pharmaceutically acceptable carrier, a CNS-penetrant NK-1 receptor antagonist

and an anxiolytic agent or antidepressant. (see specification; page 1, line 37 to page 2, line 4.)

GROUNDS FOR REJECTION TO BE REVIEWED ON APPEAL

Claims 1-16 stand rejected under 35 U.S.C 103(a)as being obvious over U.S. Patent 5,773,450 (Lowe, III et al) in view of The Merk Index List. Claims 1-16 also stand rejected provisionally under the doctrine of obviousness-type double-patenting as allegedly unpatentable over claims 1-35 of copending application 09/867,079 and claims 1-33 of copending application 09/867,357.

ARGUMENT

Rejection under Obviousness-Type Double-Patenting

In said Final Rejection the Examiner maintained the provisional rejection of claims 1-16 under obviousness-type double-patenting over claims 1-35 of then copending application 09/867,079 and claims 1-33 of then copending application 09/867,357.

Applications 09/867,079 and 09/867,357 have since been both abandoned. Accordingly, the provisional rejection made by the Examiner using these references is moot.

Rejection under 35 USC 103(a)

The Examiner finally rejected claims 1-16 under 35 USC 103(a), as being unpatentable over U.S. Patent 5,773,450 (Lowe, III et al) in view of The Merk Index List.

The Examiner noted in the Final Rejection that said rejection may be overcome by a demonstration of unexpected results. Accordingly, applicants have submitted evidence of unexpected results in a declaration contained herewith (see Evidence Appendix; exhibit A; entered by Examiner on Oct 6, 2005). The results are from a study testing the combination of an NK1 receptor antagonist and sertraline. Alone each compound produces an approximate 35% reduction in the behavior of interest. When these two doses are combined there is an 80% reduction in behavior. This suggests that at a minimum the two mechanisms are additive, that is they are working by different mechanisms that when combined produce a larger effect.

Further, Applicant's also submit a declaration (see Evidence Appendix; Exhibit B; Rule 132 Declaration also submitted concurrently herewith) as evidence of objective considerations that are probative of non-obviousness of the claimed invention. The declaration makes reference to a recent report titled "The Emerging Antidepressant Market Through 2014-Focus On Emerging Therapies And New

Indications." An excerpt from the report indicates the long felt need and forecasted commercial success of the combination of an NK1 antagonist and SSRI combination:

> GSK's (GlaxoSmithKline's) combination NK1 antagonist is of significant interest to thought leaders because recent development activity surrounding this drug shows that this class of agents, once thought to lack potential in the antidepressant market, does indeed possess competitive potential as antidepressants. GSK is developing a combination therapy of vestipitant, an NK1 receptor antagonist (also known as substance P antagonists), and paroxetine, an SSRI, for the treatment of depression and anxiety. Physician confidence in the efficacy of paroxetine, and the anticipated favorable tolerability profile of the addition of the substance P antagonists, indicates that the vestipitant/paroxetine combination pill will offer a clinically differentiated option in the crowded antidepressant market when it launches in 2011, as a result garnering peak-year sales within the $1-2 billion range. (Exhibit B, page 6)

In view of the remarks above and the evidence of unexpected results and objective considerations contained herewith, there is no valid reason why the present method invention for the treatment of depression involving a CNS-penetrant NK-1 receptor antagonist in combination with an antidepressant or an anxiolytic agent should not be fully allowable.

Reversal of the Examiner and allowance of all the claims is accordingly respectfully requested.

Respectfully submitted,

Date: 12/6/05

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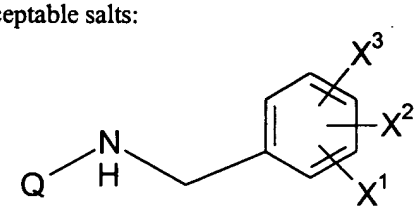
CLAIMS APPENDIX

CLAIMS

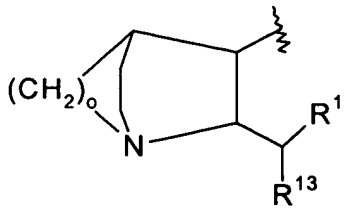
1. A pharmaceutical composition for the treatment of anxiety or depression in a mammal, comprising: (a) a compound that exhibits activity, respectively, as an anxiolytic agent or an antidepressant, or a pharmaceutically acceptable salt thereof; (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating, respectively, anxiety or depression.

2. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula I, as defined below, and their pharmaceutically acceptable salts:



I

wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;
X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6) alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and
Q is a group of the formula



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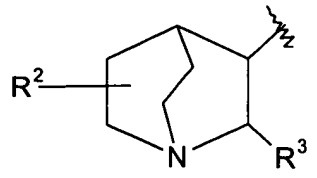

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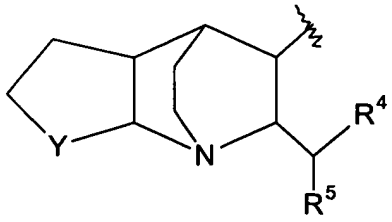

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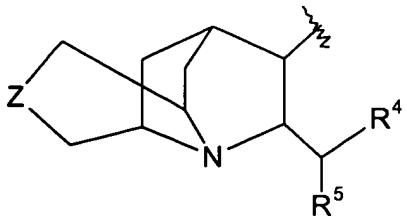

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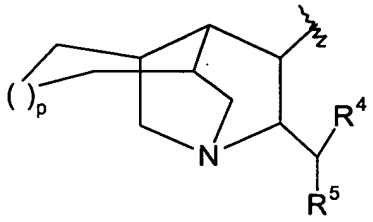

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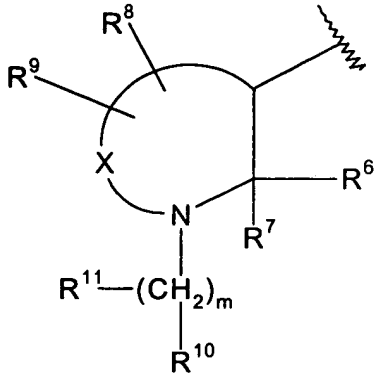
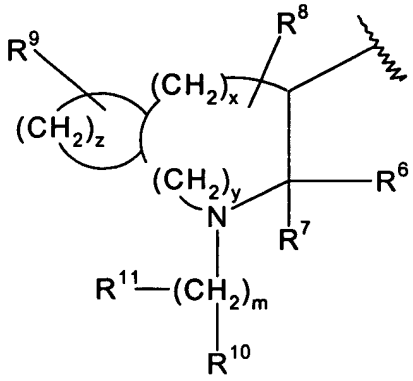


VII

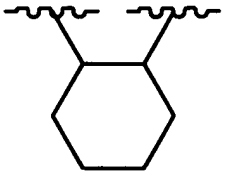
OR



VIII

wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from

one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;
R^{13} is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^1;
R^2 is hydrogen or (C_1-C_6) alkyl;
R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;
Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



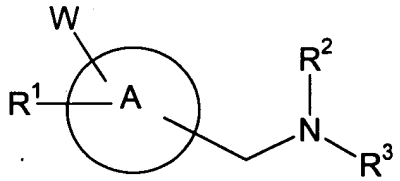
(J)

;

Z is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;
o is two or three;
p is zero or one;
R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C_1-C_3) alkoxy-carbonyl and benzyloxycarbonyl;
R^5 is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;
X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^8, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^9;
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{11};
R^6 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,(C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;
R^7 is hydrogen, phenyl or (C_1-C_6)alkyl;
or R^6 and R^7, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;
R^8 and R^9 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,-(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^6;

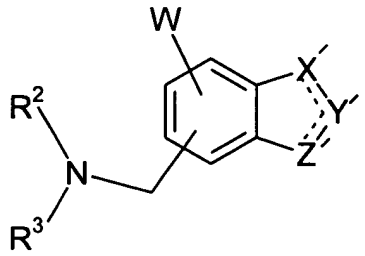
R^{10} is $NHCR^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; R^{11} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; and R^{12} is $(C_1\text{-}C_6)$alkyl, hydrogen, phenyl$(C_1\text{-}C_6)$alkyl or phenyl optionally substituted with $(C_1\text{-}C_6)$ alkyl; and with the proviso that (a) when m is 0, R^{11} is absent, (b) neither R^8, R^9, R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7, (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, and (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is independently selected from hydrogen, fluoro, $(C_1\text{-}C_6)$ alkyl, hydroxy-$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, or R^8 and R^9, together with the carbon to which they are attached, form a $(C_3\text{-}C_6)$ saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

3. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula IXa or IXb, as defined below, and their pharmaceutically acceptable salts:



IXa

or



IXb

and their pharmaceutically acceptable salts, wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the side chain containing NR^2R^3 is attached to a carbon atom of ring system A;

W is hydrogen, $(C_1\text{-}C_6)$alkyl optionally substituted with from one to three fluorine atoms, $-S(O)_v\text{-}(C_1\text{-}C_6)$ alkyl wherein v is zero, one or two, halo, benzyloxy or $(C_1\text{-}C_6)$alkoxy optionally substituted with from one to three fluorine atoms;

R^1 is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazolyl or thiophenyl), wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_6)$ alkoxy optionally substituted with from one to three fluorine atoms;

the dotted lines in formula Ib indicate that one of the X'-Y' and Y'-Z' bonds may optionally be a double bond;

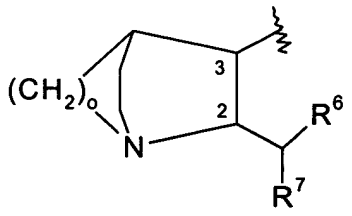
X' is selected from =CH-, $-CH_2$-, -O-, -S-, -SO-, $-SO_2$-, $-N(R^4)$-, -NH-, =N-, $-CH[(C_1\text{-}C_6)$alkyl$]$-, $=C[(C_1\text{-}C_6)$alkyl$]$-, $-CH(C_6H_5)$- and $=C(C_6H_5)$-;

Y' is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2$-, $=C[(C_1\text{-}C_6)$alkyl$]$-, $-CH[(C_1\text{-}C_6)$alkyl$]$-, $=C(C_6H_5)$-, $-CH(C_6H_5)$-, =N-, -NH-, $-N(R^4)$-, =C(halo)-, $=C(OR^4)$-, $=C(SR^4)$-, $=C(NR^4)$-, -O-, $=C(CF_3)$-, $=C(CH_2C_6H_5)$-, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)$- and $-CH(C_6H_5)$- may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said $=[(C_1\text{-}C_6)$alkyl$]$- and $-CH[C_1\text{-}C_6)$alkyl$]$- may optionally be substituted with from one to three fluorine atoms;

Z' is selected from =CH-, $-CH_2$-, =N-, -NH-, -S-, $-N(R^4)$-, $=C(C_6H_5)$-, $-CH(C_6H_5)$-, $=C[(C_1\text{-}C_6)$ alkyl$]$- and $-CH[(C_1\text{-}C_6)$alkyl$]$-;

or X', Y' and Z', together with the two carbon atoms shared between the benzo ring and the X'Y'Z' ring, form a fused pyridine or pyrimidine ring;

R^2 is hydrogen or $-CO_2(C_1-C_{10})$alkyl;
R^3 is selected from



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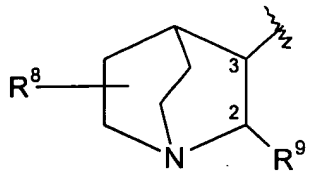

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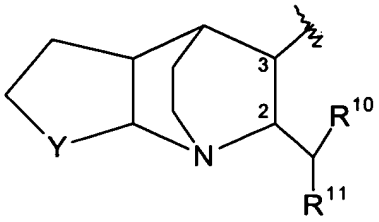

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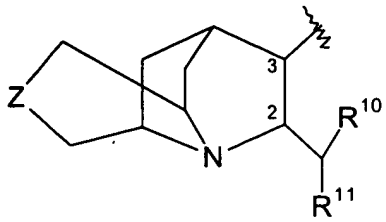

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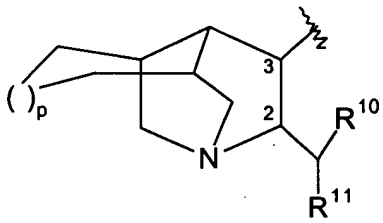

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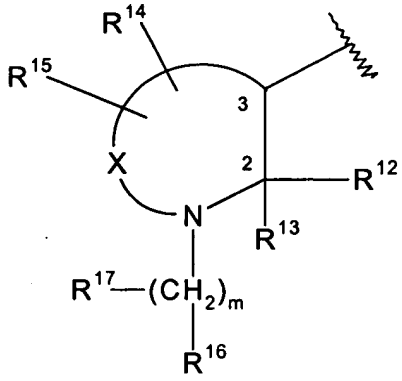

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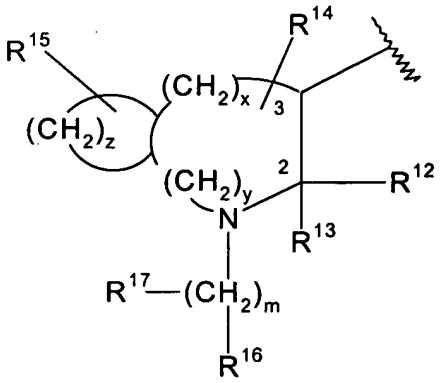
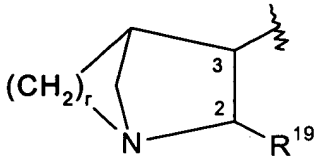


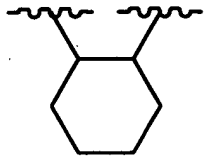
XVI

and



XVII

wherein R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said phenyl may optionally be substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and $(C_1\text{-}C_3)$ alkoxy-carbonyl;
R^4 is $(C_1\text{-}C_6)$ alkyl or phenyl;
R^7 is selected from $(C_3\text{-}C_4)$ branched alkyl, $(C_5\text{-}C_6)$ branched alkenyl, $(C_5\text{-}C_7)$ cycloalkyl, and the radicals named in the definition of R^6;
R^8 is hydrogen or $(C_1\text{-}C_6)$ alkyl;
R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;
Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



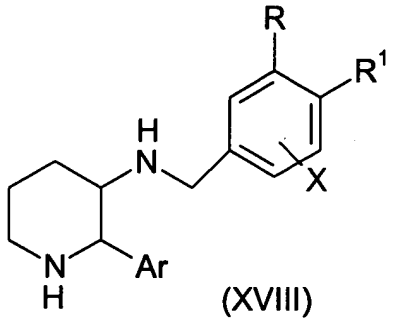
(J)

;

Z is oxygen, sulfur, amino, $(C_1\text{-}C_3)$alkylamino or $(CH_2)_n$ wherein n is zero, one or two;
x is zero, one or two;
y is zero, one or two;
z is three, four or five;
o is two or three;
p is zero or one;
r is one, two or three;
the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbon atoms of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;
R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms and $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms;
X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};
R^{12} is a radical selected from hydrogen, $(C_1\text{-}C_6)$ straight or branched alkyl, $(C_3\text{-}C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-$(C_2\text{-}C_6)$ alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-$(C_2\text{-}C_6)$ alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, $(C_1\text{-}C_{10})$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_{10})$ alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$-alkylamino, $(C_1\text{-}C_6)$alkyl-O-C(=O)-, $(C_1\text{-}C_6)$alkyl-O-C(=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)-O-, $(C_1\text{-}C_6)$alkyl-C(=O)-$(C_1\text{-}C_6)$alkyl-O-, $(C_1\text{-}C_6)$alkyl-C(=O)-, $(C_1\text{-}C_6)$alkyl-C(=O)-, $(C_1\text{-}C_6)$alkyl-, di-$(C_1\text{-}C_6)$alkylamino, -C(=O)-NH-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$-alkyl-C(=O)-NH-$(C_1\text{-}C_6)$alkyl, -NHC(=O)H and –NHC(=O)-$(C_1\text{-}C_6)$alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;
R^{13} is hydrogen, phenyl or $(C_1\text{-}C_6)$alkyl;
or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to such point of attachment may optionally be replaced by oxygen, nitrogen or sulfur;

R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};
R^{16} is $NHC(=O)R^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};
R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and
R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;
with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula XVI, R^{14} and R^{15} cannot be attached to the same carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, (C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} can not both be hydrogen, and (e) when R^{14} or R^{15} is attached to a carbon atom of X or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom.

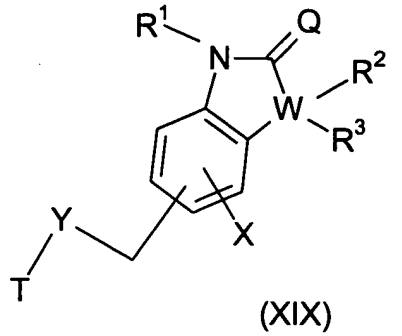
4. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XVIII, as depicted and defined below, and their pharmaceutically acceptable salts:



(XVIII)

wherein R is halo (C_1-C_8)alkyl, halo (C_2-C_8)alkenyl, halo (C_2-C_8)alkynyl or halo (C_1-C_8)alkyl substituted by hydroxy or (C_1-C_8)alkoxy; R^1 is hydrogen, halo or (C_1-C_6)alkoxy; or
R and R^1, together with the two carbon atoms shared between the benzene ring and the R and R^1, complete a fused (C_4-C_6)cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are optionally substituted by up to five subtituents selected from halo, (C_1-C_6)alkyl and halo (C_1-C_6)alkyl;
X is (C_1-C_6)alkoxy, halo (C_1-C_6)alkoxy, phenoxy or halo; and
Ar is phenyl optionally substituents by halo.

5. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XIX, as depicted and defined below, and their pharmaceutically acceptable salts:

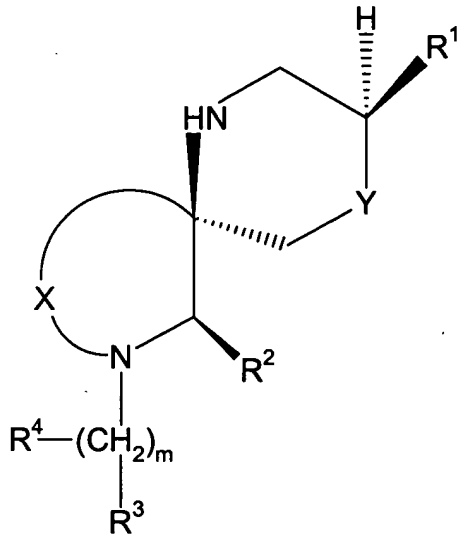


(XIX)

wherein

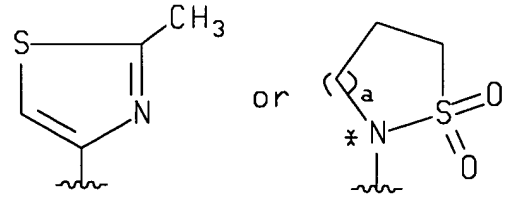
W is methylene, ethylene, propylene, vinylene, $-CH_2-O-$,$-O-CH_2-$, $-CH_2-S-$ or $-S-CH_2-$;
R^1, R^2 and R^3 are independently hydrogen, (C_1-C_3) alkyl, (C_1-C_3) alkoxy or halo (C_1-C_3) alkyl, provided that when W is methylene, both R^2 and R^3 are not hydrogen;
X is halo, (C_1-C_3) alkoxy, (C_1-C_3) alkoxy or (C_1-C_3) alkenyl;
Y is imino or oxy;
Q is oxygen or sulfur; and
T is (2S,3S)-2-diphenylmethylquinuclidin-3-yl,(2S,3S)-2-phenylpiperdin-3-yl or (2S,3S)-2-diphenylmethyl-1-azanorbornan-3-yl.

6. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XX, as depicted and defined below, and their pharmaceutically acceptable salts:



XX

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, $-C(=O)-NH-(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$C(=O)-NH-(C_1-C_6)$ alkyl, hydroxy(C_1-C_4)alkyl,$-NHC(=O)H$, $-NHC(=O)-(C_1-C_6)$ alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-S(O)_v-(C_1-C_{10})$-alkyl wherein v is zero, one or two, $-S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, $-SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, $(SO_2-(C_1-C_{10})$alkyl) $((C_1-C_{10})$alkyl)N wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, $-N(SO_2-(C_1-C_{10})alkyl)_2$ and $(SO_2-$aryl) $((C_1-C_{10})$alkyl)N; and wherein the aryl moieties of said $-S(O)_v$-aryl, -O-aryl and $(SO_2-$aryl) $((C_1-C_{10})$alkyl)N are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;
or R^1 is phenyl substituted with a group having the formula



wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;
R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and

the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;

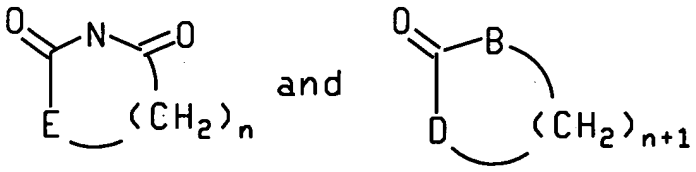
R^3 is selected from $NHC(=O)R^8$, $NHCH_2R^8$, SO_2R^8, AR^5, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;

A is CH_2, nitrogen, oxygen, sulfur or carbonyl;

R^8 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;

R^5 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with (C_1-C_6)alkyl or (C_2-C_6) spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a (C_3-C_5) fused carbocyclic ring;

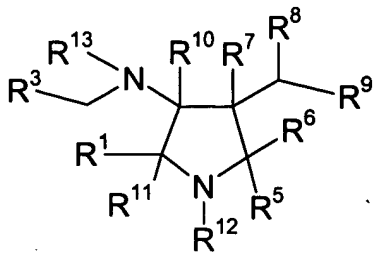
X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;

R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl- and the radicals set forth in the definition of R^2; and

Y is $(CH_2)_z$ wherein z is zero or one;

with the proviso that: (a) when A is -(CH_2)- or carbonyl, R^5 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom;

7. A pharmaceutical composition according to claim 1, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XXI, as depicted and defined below, and their pharmaceutically acceptable salts:



XXI

wherein R^1 is selected from hydrogen, $(C_1\text{-}C_6)$ straight or branched alkyl, $(C_3\text{-}C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl $(C_2\text{-}C_6)$ alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl $(C_2\text{-}C_6)$ alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_6)$ alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy), $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkyl-O-C(=O)-, $(C_1\text{-}C_6)$alkyl-O-C(=O)- $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)-O-, $(C_1\text{-}C_6)$alkyl-C-, $(C_1\text{-}C_6)$alkyl-O-, $(C_1\text{-}C_6)$alkyl-C(=O)-, $(C_1\text{-}C_6)$alkyl-C(=O)-, $(C_1\text{-}C_6)$alkyl-, di-$(C_1\text{-}C_6)$alkylamino, -C(=O)NH-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)-NH-$(C_1\text{-}C_6)$alkyl-, -NHC(=O)H and –NHC(=O)-$(C_1\text{-}C_6)$ alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said $(C_3\text{-}C_7)$ cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to three fluorine atoms, $(C_1\text{-}C_6)$ alkoxy, amino, phenyl, trihaloalkoxy (e.g., trifluoromethoxy), $(C_1\text{-}C_6)$ alkylamino, -C(=O)-NH-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)- -C-O-$(C_1\text{-}C_6)$alkyl, -C(=O)H, $-CH_2OR^{13}$, NH$(C_1\text{-}C_6)$alkyl-, -NHC(=O)H, $-NR^{24}$C-$(C_1\text{-}C_6)$alkyl and –NHC(=O)-$(C_1\text{-}C_6)$alkyl;

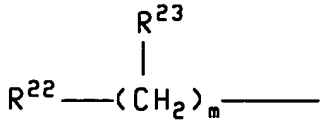
one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_8)$acyloxy$(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_8)$alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, $(C_1\text{-}C_3)$alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, HC(=O)-, $R^{14}R^{15}NCO_2CH_2$-, $R^{16}OCO_2CH_2$-, $(C_1\text{-}C_4)$alkyl-CO_2CH_2-, $-CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2$-, $R^{19}OCO_2$-, $C_6H_5CH_2CO_2CH_2$-, $C_6H_5CO_2CH_2$-, $(C_1\text{-}C_4)$alkyl-CH(OH)-, $C_6H_5CH(OH)$-, $C_6H_5CH_2CH(OH)$-, CH_2halo, $R^{20}SO_2OCH_2$, $-CO_2R^{16}$ and $R^{21}CO_2$-;

R^{10} and R^{11} are independently selected from hydrogen, $(C_1\text{-}C_3)$ alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula



wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23} (as indicated by the slanted line to R^{23} which intersects the horizontal line to $(CH_2)_m$ in the above figure);

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, $(C_1\text{-}C_3)$alkyl and phenyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino, di-$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$-alkyl-O-C(=O)-, $(C_1\text{-}C_6)$alkyl-O-C(=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)- $(C_1\text{-}C_6)$alkyl-C(=O)-$(C_1\text{-}C_6)$alkyl-O-, $(C_1\text{-}C_6)$alkyl-C-, $(C_1\text{-}C_6)$-alkyl-C(=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$ straight or branched alkyl, $(C_3\text{-}C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-$(C_2\text{-}C_6)$alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl

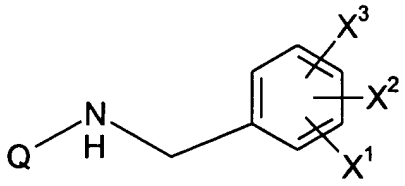
moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O), (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged.

8. A method of treating anxiety or depression in a mammal, comprising administering to said mammal an antianxiety effective amount or an antidepressant effective amount, respectively, of a pharmaceutical composition according to claims 1, 2, 3, 4, 5, 6, or 7.

9. A method of treating anxiety or depression in a mammal, comprising administering to said mammal: (a) a compound that exhibits activity as an anxiolytic antianxiety agent or an antidepressant, or a pharmaceutically acceptable salt thereof; and (b) a CNS-penetrant NK-1 receptor antagonist or pharmaceutically acceptable salt thereof; wherein the active agents "a" and "b" above are present in amounts that render the combination of the two agents effective in treating, respectively, anxiety or depression.

10. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula I, as depicted and defined below, and their pharmaceutically acceptable salts:

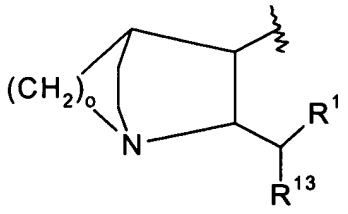


I

wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms or (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6) alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and

Q is a group of the formula



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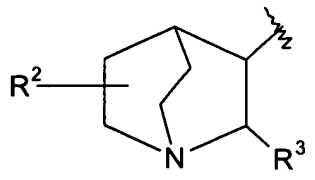
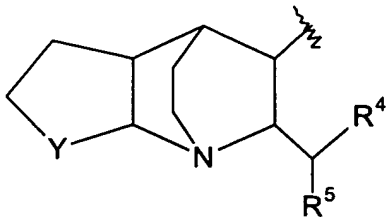


III



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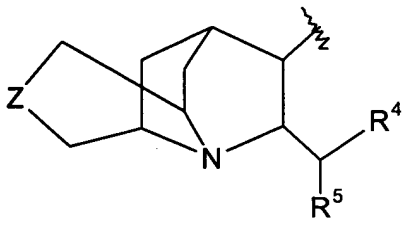

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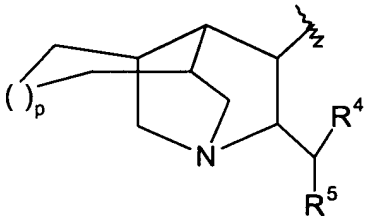

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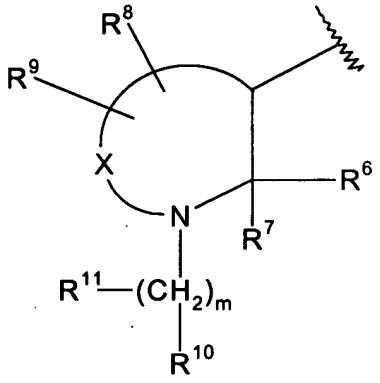
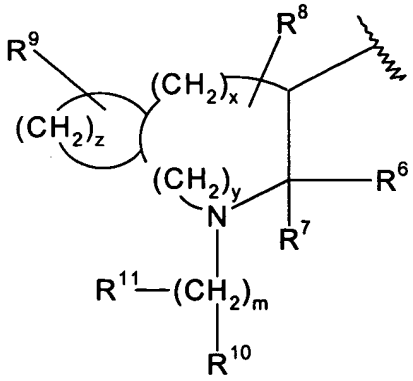


VII

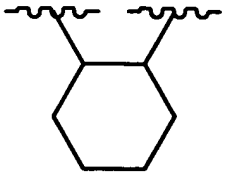
OR



VIII

wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from

one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;
R^{13} is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^1;
R^2 is hydrogen or (C_1-C_6) alkyl;
R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;
Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



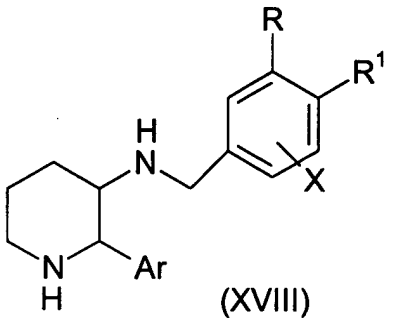
(J)

;

Z is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;
o is two or three;
p is zero or one;
R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C_1-C_3) alkoxy-carbonyl and benzyloxycarbonyl;
R^5 is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;
X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^8, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^9;
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{11};
R^6 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl,(C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and -NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;
R^7 is hydrogen, phenyl or (C_1-C_6)alkyl;
or R^6 and R^7, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;
R^8 and R^9 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl,-(C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^6;

R^{10} is $NHCR^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; R^{11} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^6, R^8 and R^9; and R^{12} is (C_1-C_6)alkyl, hydrogen, phenyl(C_1-C_6)alkyl or phenyl optionally substituted with (C_1-C_6) alkyl; and with the proviso that (a) when m is 0, R^{11} is absent, (b) neither R^8, R^9, R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7, (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, and (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is independently selected from hydrogen, fluoro, (C_1-C_6) alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^8 and R^9, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

11. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XVIII, as depicted and defined below, and their pharmaceutically acceptable salts:

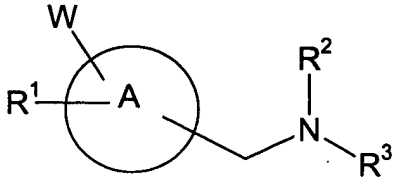


(XVIII)

wherein R is halo (C_1-C_8)alkyl, halo (C_2-C_8)alkenyl, halo (C_2-C_8)alkynyl or halo (C_1-C_8)alkyl substituted by hydroxy or (C_1-C_8)alkoxy; R^1 is hydrogen, halo or (C_1-C_6)alkoxy; or
R and R^1, together with the two carbon atoms shared between the benzene ring and the R and R^1, complete a fused (C_4-C_6)cycloalkyl wherein one carbon atom is optionally replaced by oxygen and wherein one or two of the carbon atoms are optionally substituted by up to five subtituents selected from halo, (C_1-C_6)alkyl and halo (C_1-C_6)alkyl;
X is (C_1-C_6)alkoxy, halo (C_1-C_6)alkoxy, phenoxy or halo; and
Ar is phenyl optionally substituents by halo.

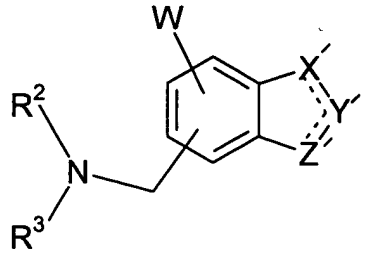
12. A method according to claim 11, wherein the NK-1 receptor antagonist is administered in an amount ranging from about 5 mg per day to about 200 mg per day.

13. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula IXa or IXb, as depicted and defined below, and their pharmaceutically acceptable salts:



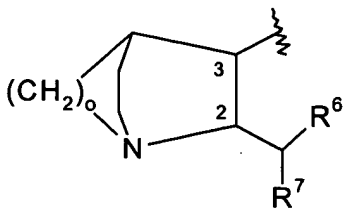
IXa

or



IXb

wherein A is a ring system selected from phenyl, naphthyl, thienyl, quinolinyl and indolinyl, and wherein the side chain containing NR^2R^3 is attached to a carbon atom of ring system A;
W is hydrogen, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, $-S(O)_v-(C_1-C_6)$ alkyl wherein v is zero, one or two, halo, benzyloxy or (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms;
R^1 is a 4, 5 or 6 membered heterocyclic ring containing from one to three heteroatoms selected from oxygen, nitrogen and sulfur (e.g., thiazolyl, azetidinyl, pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxazolyl, pyridyl, pyrimidinyl, pyrazolyl or thiophenyl), wherein said heterocyclic ring may contain from zero to three double bonds and may optionally be substituted with one or more substituents, preferably one or two substituents, independently selected from (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_6) alkoxy optionally substituted with from one to three fluorine atoms;
the dotted lines in formula Ib indicate that one of the X'-Y' and Y'-Z' bonds may optionally be a double bond;
X' is selected from =CH-, $-CH_2-$, -O-, -S-, -SO-, $-SO_2-$, $-N(R^4)-$, -NH-, =N-, $-CH[(C_1-C_6)alkyl]-$, $=C[(C_1-C_6)alkyl]-$, $-CH(C_6H_5)-$ and $=C(C_6H_5)-$;
Y' is selected from C=O, $C=NR^4$, C=S, =CH-, $-CH_2-$, $=C[(C_1-C_6)alkyl]-$, $-CH[(C_1-C_6)alkyl]-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, =N-, -NH-, $-N(R^4)-$, =C(halo)-, $=C(OR^4)-$, $=C(SR^4)-$, $=C(NR^4)-$, -O-, $=C(CF_3)-$, $=C(CH_2C_6H_5)-$, -S- and SO_2, wherein the phenyl moieties of said $=C(C_6H_5)-$ and $-CH(C_6H_5)-$ may optionally be substituted with from one to three substituents independently selected from trifluoromethyl and halo, and wherein the alkyl moieties of said $=[(C_1-C_6)alkyl]-$ and $-CH[C_1-C_6)alkyl]-$ may optionally be substituted with from one to three fluorine atoms;
Z' is selected from =CH-, $-CH_2-$, =N-, -NH-, -S-, $-N(R^4)-$, $=C(C_6H_5)-$, $-CH(C_6H_5)-$, $=C[(C_1-C_6)$ alkyl]- and $-CH[(C_1-C_6)alkyl]-$;
or X', Y' and Z', together with the two carbon atoms shared between the benzo ring and the X'Y'Z' ring, form a fused pyridine or pyrimidine ring;
R^2 is hydrogen or $-CO_2(C_1-C_{10})alkyl$;
R^3 is selected from



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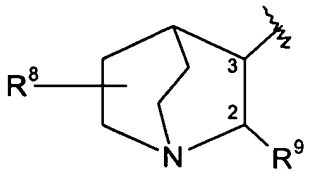
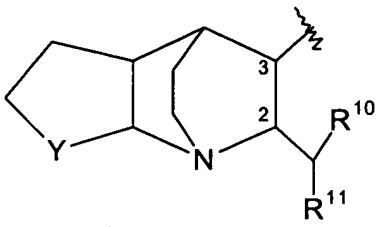
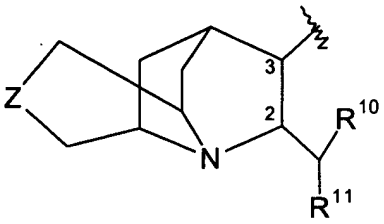


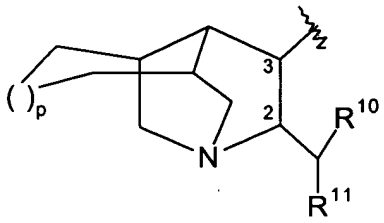
XI



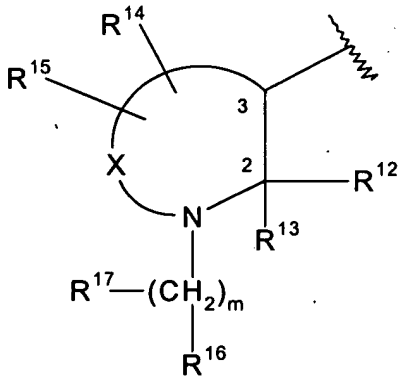
XII



XIII



XIV



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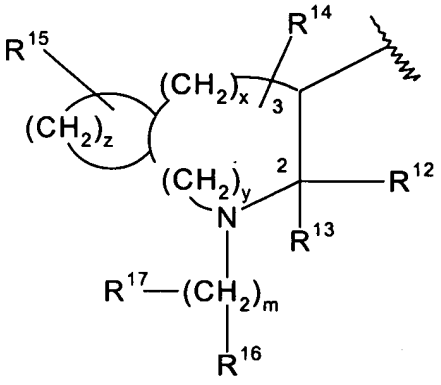
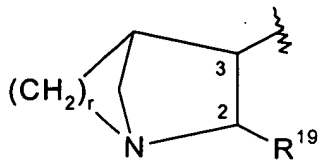


XVI

and

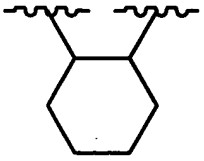


XVII

wherei

n R^6 and R^{10} are independently selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl, wherein said

phenyl may optionally be substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;
R^4 is (C_1-C_6) alkyl or phenyl;
R^7 is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named in the definition of R^6;
R^8 is hydrogen or (C_1-C_6) alkyl;
R^9 and R^{19} are independently selected from phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl and furyl, and R^9 and R^{19} may optionally be substituted with from one to three substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;
Y is $(CH_2)_l$ wherein l is an integer from one to three, or Y is a group of the formula



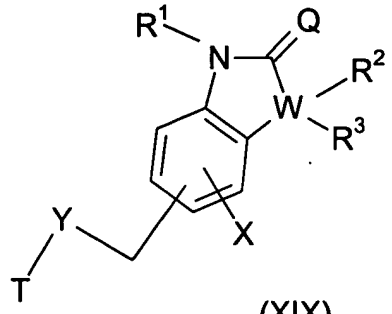
(J)

;

Z is oxygen, sulfur, amino, (C_1-C_3)alkylamino or $(CH_2)_n$ wherein n is zero, one or two;
x is zero, one or two;
y is zero, one or two;
z is three, four or five;
o is two or three;
p is zero or one;
r is one, two or three;
the ring containing $(CH_2)_z$ may contain from zero to three double bonds, and one of the carbon atoms of $(CH_2)_z$ may optionally be replaced by oxygen, sulfur or nitrogen;
R^{11} is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;
X is $(CH_2)_q$ wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{14}, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^{15};
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(CH_2)_m$ chain, may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{17};
R^{12} is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6) alkyl, benzhydryl and benzyl, wherein the point of attachment on R^{12} is a carbon atom unless R^{12} is hydrogen, and wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;
R^{13} is hydrogen, phenyl or (C_1-C_6)alkyl;
or R^{12} and R^{13}, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms that is neither the point of attachment of the spiro ring nor adjacent to such point of attachment may optionally be replaced by oxygen, nitrogen or sulfur;

R^{14} and R^{15} are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, -C(=O)-OH, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-, and the radicals set forth in the definition of R^{12};
R^{16} is $NHC(=O)R^{18}$, $NHCH_2R^{18}$, SO_2R^{18}, CO_2H or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15};
R^{17} is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^{12}, R^{14} and R^{15}; and
R^{18} is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;
with the proviso that (a) when m is 0, one of R^{16} and R^{17} is absent and the other is hydrogen, (b) when R^3 is a group of the formula XVI, R^{14} and R^{15} cannot be attached to the same carbon atom, (c) when R^{14} and R^{15} are attached to the same carbon atom, then either each of R^{14} and R^{15} is independently selected from hydrogen, fluoro, (C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl and (C_1-C_6)alkoxy-(C_1-C_6)alkyl, or R^{14} and R^{15}, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached; (d) R^{12} and R^{13} can not both be hydrogen, and (e) when R^{14} or R^{15} is attached to a carbon atom of X or $(CH_2)_y$ that is adjacent to the ring nitrogen, then R^{14} or R^{15}, respectively, must be a substituent wherein the point of attachment is a carbon atom.

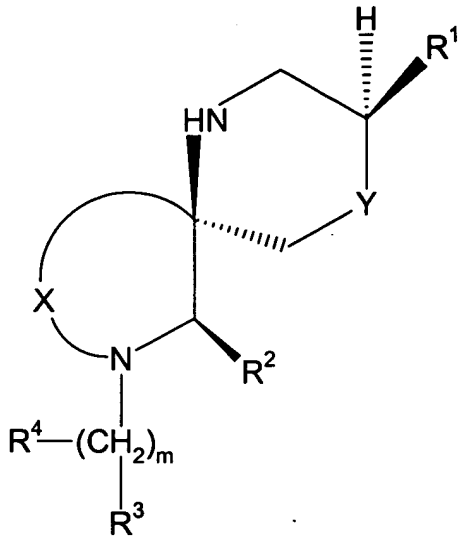
14. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XIX, as depicted and defined below, and their pharmaceutically acceptable salts:



(XIX)

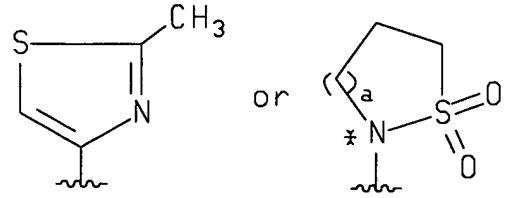
wherein
W is methylene, ethylene, propylene, vinylene, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$ or $-S-CH_2-$;
R^1, R^2 and R^3 are independently hydrogen, (C_1-C_3) alkyl, (C_1-C_3) alkoxy or halo (C_1-C_3) alkyl, provided that when W is methylene, both R^2 and R^3 are not hydrogen;
X is halo, (C_1-C_3) alkoxy, (C_1-C_3) alkoxy or (C_1-C_3) alkenyl;
Y is imino or oxy;
Q is oxygen or sulfur; and
T is (2S,3S)-2-diphenylmethylquinuclidin-3-yl,(2S,3S)-2-phenylpiperdin-3-yl or (2S,3S)-2-diphenylmethyl-1-azanorbornan-3-yl.

15. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XX, as depicted and defined below, and their pharmaceutically acceptable salts:



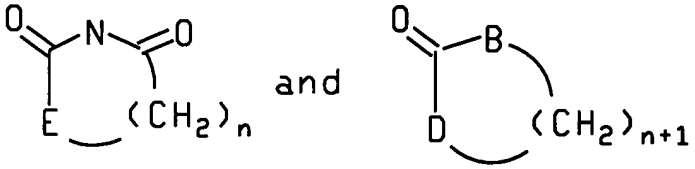
XX

wherein R^1 is phenyl optionally substituted with one or more substituents, preferably with from one to three substituents, independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6)-alkylamino, di-(C_1-C_6)alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6) alkyl, hydroxy(C_1-C_4)alkyl,-NHC(=O)H, -NHC(=O)-(C_1-C_6) alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -$S(O)_v$-(C_1-C_{10})-alkyl wherein v is zero, one or two, -$S(O)_v$-aryl wherein v is zero, one or two, -O-aryl, -$SO_2NR^4R^5$ wherein each of R^4 and R^5 is, independently, (C_1-C_6)alkyl, or R^4 and R^5, together with the nitrogen to which they are attached, form a saturated ring containing one nitrogen and from 3 to 6 carbons, $(SO_2-(C_1-C_{10})$alkyl) $((C_1-C_{10})$alkyl)N wherein one or both of the alkyl moieties may optionally be substituted with from one to three fluorine atoms, -$N(SO_2-(C_1-C_{10})$alkyl$)_2$ and $(SO_2-$aryl) $((C_1-C_{10})$alkyl)N; and wherein the aryl moieties of said -$S(O)_v$-aryl, -O-aryl and $(SO_2-$aryl) $((C_1-C_{10})$alkyl)N are independently selected from phenyl and benzyl and may optionally be substituted with from one to three substituents independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy and halo;
or R^1 is phenyl substituted with a group having the formula



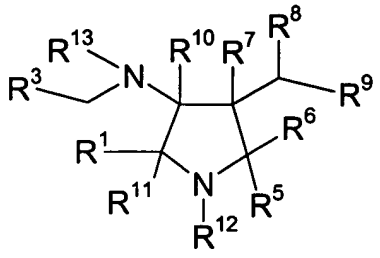
wherein a is 0, 1 or 2 and the asterisk represents a position meta to the point of attachment of R^1;
R^2 is selected from (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents, preferably with from one to three substituents, independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, amino, hydroxy-(C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;
m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom in the $(CH_2)_m$ chain, may optionally

be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^4;
R^3 is selected from $NHC(=O)R^8$, $NHCH_2R^8$, SO_2R^8, AR^5, CO_2H and the radicals set forth in the definitions of R^2, R^6 and R^7;
A is CH_2, nitrogen, oxygen, sulfur or carbonyl;
R^8 is $(C_1\text{-}C_6)$alkyl, hydrogen, phenyl or phenyl $(C_1\text{-}C_6)$alkyl;
R^4 is selected from oximino (=NOH) and the radicals set forth in the definitions of R^2, R^6 and R^7;
R^5 is a monocyclic or bicyclic heterocycle selected from the group consisting of pyrimidinyl, benzoxazolyl, 2,3-dihydro-3-oxobenzisosulfonazol-2-yl, morpholin-1-yl, thiomorpholin-1-yl, benzofuranyl, benzothienyl, indolyl, isoindolyl, isoquinolinyl, furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl, thienyl, and groups of the formulae



wherein B and D are selected from carbon, oxygen and nitrogen, and at least one of B and D is other than carbon; E is carbon or nitrogen; n is an integer from 1 to 5; any one of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be optionally substituted with $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$ spiroalkyl; and either any one pair of the carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may be bridged by a one or two carbon atom linkage, or any one pair of adjacent carbon atoms of said $(CH_2)_n$ and $(CH_2)_{n+1}$ may form, together with from one to three carbon atoms that are not members of the carbonyl containing ring, a $(C_3\text{-}C_5)$ fused carbocyclic ring;
X is $(CH_2)_q$ wherein q is two or three and wherein one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^6, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^7;
R^6 and R^7 are independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), cyano, hydroxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino, di-$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkoxy, -C(=O)-OH, $(C_1\text{-}C_6)$alkyl-O-C(=O)-, $(C_1\text{-}C_6)$alkyl-O-C(=O)-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-C(=O)-O-, $(C_1\text{-}C_6)$alkyl-C(=O)-$(C_1\text{-}C_6)$alkyl-O-, $(C_1\text{-}C_6)$alkyl-C-, $(C_1\text{-}C_6)$alkyl-C(=O)-$(C_1\text{-}C_6)$alkyl- and the radicals set forth in the definition of R^2; and
Y is $(CH_2)_z$ wherein z is zero or one;
with the proviso that: (a) when A is -(CH_2)- or carbonyl, R^5 cannot be furyl, pyridyl, isothiazolyl, oxazolyl, triazolyl, tetrazolyl, quinolyl, thiazolyl or thienyl; (b) when m is zero, one of R^3 and R^4 is absent and the other is hydrogen; and (c) when R^6 or R^7 is attached to a carbon atom of X that is adjacent to the ring nitrogen, then R^6 or R^7, respectively, must be a substituent wherein the point of attachment is a carbon atom.

16. A method according to claim 9, wherein the NK-1 receptor antagonist or pharmaceutically acceptable salt thereof is selected from compounds of the formula XXI, as depicted and defined below, and their pharmaceutically acceptable salts:



XXI

wherein R^1 is selected from hydrogen, $(C_1\text{-}C_6)$ straight or branched alkyl, $(C_3\text{-}C_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl $(C_2\text{-}C_6)$ alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl $(C_2\text{-}C_6)$ alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, $(C_1\text{-}C_6)$ alkyl

optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6)alkylamino, (C_1-C_6)alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)- (C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-NH-(C_1-C_6)alkyl-, -NHC(=O)H and –NHC(=O)-(C_1-C_6) alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6) alkoxy, amino, phenyl, trihaloalkoxy (e.g., trifluoromethoxy), (C_1-C_6) alkylamino, -C(=O)-NH-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- -C-O-(C_1-C_6)alkyl, -C(=O)H, -CH_2OR^{13}, NH(C_1-C_6)alkyl-, -NHC(=O)H, -NR^{24}C-(C_1-C_6)alkyl and –NHC(=O)-(C_1-C_6)alkyl;

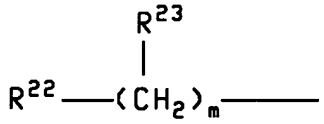
one of R^5 and R^6 is hydrogen and the other is selected from hydroxymethyl, hydrogen, (C_1-C_3)alkyl, (C_1-C_8)acyloxy(C_1-C_3)alkyl, (C_1-C_8)alkoxymethyl and benzyloxymethyl;

R^7 and R^8 are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^9 is selected from methyl, hydroxymethyl, HC(=O)-, $R^{14}R^{15}NCO_2CH_2$-, $R^{16}OCO_2CH_2$-, (C_1-C_4)alkyl-CO_2CH_2-, -$CONR^{17}R^{18}$, $R^{17}R^{18}NCO_2$-, $R^{19}OCO_2$-, $C_6H_5CH_2CO_2CH_2$-, $C_6H_5CO_2CH_2$-, (C_1-C_4)alkyl-CH(OH)-, $C_6H_5CH(OH)$-, $C_6H_5CH_2CH(OH)$-, CH_2halo, $R^{20}SO_2OCH_2$, -CO_2R^{16} and $R^{21}CO_2$-;

R^{10} and R^{11} are independently selected from hydrogen, (C_1-C_3) alkyl and phenyl;

R^{12} is hydrogen, benzyl or a group of the formula



wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(CH_2)_m$ may optionally be substituted with R^{23} (as indicated by the slanted line to R^{23} which intersects the horizontal line to $(CH_2)_m$ in the above figure);

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{24} are independently selected from hydrogen, (C_1-C_3)alkyl and phenyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C_1-C_6)alkyl, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, (C_1-C_6)-alkyl-O-C(=O)-, (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)- (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)-alkyl-C(=O)-(C_1-C_6)alkyl, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-(C_2-C_6)alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-(C_2-C_6)alkyl and benzhydryl may optionally be substituted with one or two substituents independently selected from halo, nitro, (C_1-C_6)alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_6)alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-C(=O), (C_1-C_6)alkyl-O-C(=O)-(C_1-C_6)alkyl, (C_1-C_6)alkyl-C(=O)-O-, (C_1-C_6)alkyl-C(=O)-(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C(=O)-, (C_1-C_6)alkyl-C-(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -C(=O)NH-(C_1-C_6)alkyl, (C_1-C_6)-alkyl-C(=O)-NH-(C_1-C_6)alkyl, -NHC(=O)H and –NHC(=O)-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

or R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached form a second pyrrolidine ring; with the proviso that when R^9, together with the carbon to which it is attached, the nitrogen of the pyrrolidine ring, the carbon to which R^7 is attached and the carbon to which R^5 and R^6 are attached, form a second pyrrolidine ring (thus forming a bicyclic structure containing a bridgehead nitrogen), either R^{12} is absent or R^{12} is present and the nitrogen of the second pyrrolidine ring is positively charged.

EVIDENCE APPENDIX

Exhibit A: Rule 132 Declaration (unexpected results for an combination composition of an NK1 antagonist and a serotonin selective reuptake inhibitor)

Exhibit B: Rule 132 Declaration (Cognos Plus Study #11: The Emerging Antidepressant Market Through 2014-Focus On Emerging Therapies And New Indications")

Exhibit A

Patent Application
Attorney Docket No. PC10408A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 4th day of October, 2005.

By _____
(Signature of person mailing)
Jason G. Tebbutt
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Susan B. Sobolov-Jaynes :
Examiner: Jarvis, W.
APPLICATION NO.: 09/707,320 :
Group Art Unit: 1614
FILING DATE: November 7, 2000 :

TITLE: COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY :

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 132 DECLARATION

Stafford McLean hereby, declares, states and says that:

1) He received a Ph.D. from Princeton University

2) He is currently employed by Pfizer Inc in Pfizer's Research and Development Division as a Research Fellow in the Department of Neuroscience in Bldg 220 Rm 4471 and he has worked as a research scientist at Pfizer for 19 years

3) He is familiar with the subject matter of the above identified application and the references cites therein and was a principal investigator directing both *in vitro* and *in vivo* research involving NK_1 receptors. An in vivo model relevant to anxiety and obsessive compulsive disorder was established to assess the effects of antagonists of the NK_1 receptor, Serotonin Reuptake Inhibitors and their combination, therein. Rodents, using the bedding material in their cages, will bury noxious materials and this burying behavior is inhibited by agents with anxiolytic activity. This burying behavior extends to "harmless" object and is blocked by anxiolytic agents, as well. The SRI, sertraline, is active in this model producing a maximal effect at 32 mg/kg, s.c. Similarly, an NK_1 receptor antagonist is active in the model with a maximal effect at 32 mg/kg, s.c.

Combination of said agents at lower doses that are modestly active results in a maximal blockade of the burying behavior. This suggests the opportunity to combine agents with NK_1 activity and agents with serotonin reuptake activity either as separate drugs or combined into a single molecule to produce robust anxiolytic activity. Furthermore, reduction in dose/activity of each agent may reduce the likelihood of unwanted side effects.

4) Further declarant sayeth not.

He further declares that all statements made herein of his own knowledge are true and all statements made on information and belief to be true. All statements made herein are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code, and that willful false statements may jeopardize the validity of the above application or any patent that may issue from it.

Date: 9-15-05

Stafford McLean

Date: June 15, 2005

Male ICR mice (17-19 g) upon arrival were grouped housed (10/box) and allowed to habituate to the vivarium for approximately 1 week. On the day of the study, mice were numbered (tail), weighed and injected with drug of interest. Thirty minutes later, mice were placed in a small mouse box (11.5 x 7.25 x 4.75") which had 25 marbles that were equally spaced on top of ~5 cm of sawdust bedding. Mice were allowed to explore/bury for 30 minutes. At the end of time, mice were removed from the box and the number of marbles that were at least 1/3 way visible were counted and recorded. Data is expressed as the number of marbles buried (not visible). Immediately after removing mice from the box, they were placed 5 at a time on a wire grid to measure the degree to which they might be behaviorally impaired. The grid was then inverted for 45 seconds. The mice were rated as either falling off (0), hanging on (1) or climbed on top (2). This measure was done as an indicator of impairment/sedation. Experimenter was blind to drug conditions until end of study and groups were distributed evenly throughout the rack.

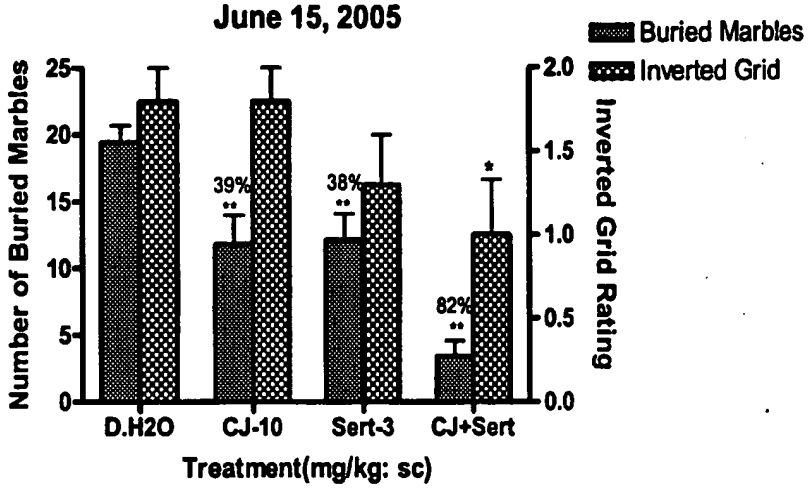
Drugs/doses: **CJ-011974-01 (10 mg/kg;sc) and/or Sertraline (3 mg/kg;sc)**
Route of Admin: **SC**
Vehicle: D. H2O
Pre-treat: **30 minutes for MB & 60 min for IG**
Comments:

Mouse #	Vehicle		CJ-11974		Sertraline		CJ+Sert	
	marble	grid	marble	grid	marble	grid	marble	grid
1	21	2	18	2	17	2	11	2
2	19	2	9	2	7	2	8	2
3	23	2	21	2	12	0	0	0
4	21	2	2	0	16	1	4	2
5	17	0	9	2	6	0	4	0
6	17	2	21	2	12	2	3	0
7	20	2	16	2	0	2	0	0
8	10	2	7	2	14	0	1	2
9	23	2	4	2	22	2	3	2
10	23	2	11	2	15	2	0	0
Mean	19.4	1.8	11.8	1.8	12.1	1.3	3.4	1.0
SEM	1.3	0.2	2.2	0.2	2.0	0.3	1.2	0.3
Sig from Veh			$		$		$	$
% inhibition			39%		38%		82%	

Conclusion: Previous work has shown a dose-dependent decrease in marble burying by sertraline and CJ-11974, an NK_1 receptor antagonist. Such decrease is consistent with the activity exhibited by other anxiolytics in this assay and is consistent with the anxiolysis observed with these two agents in the clinic. Combined dosing of sertraline and CJ-11974, at doses that when given alone produce only a modest effect, provides a near maximal response. This is consistent with an additive response. As seen in the graphical representation of the data (below) the combined doses also produce a

significant effect on the inverted grid suggesting some impairment of sensorimotor function. The contribution of this to the reduction in marble burying will be further explored.

Effects of CJ-11974 and/or Sertraline on Marble Burying Behavior & the Inverted Grid in Male ICR Mice
June 15, 2005



* p< 0.05; **p<0.01 vs. appropriate vehicle control
n=10

Exhibit B

Patent Application
Attorney Docket No. PC10408A

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 6th day of December, 2005.

By _____
(Signature of person mailing)
Jason G. Tebbutt
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Susan B. Sobolov-Jaynes : Examiner: Jarvis, W.

APPLICATION NO.: 09/707,320 : Group Art Unit: 1614

FILING DATE: November 7, 2000 :

TITLE: COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY :

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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4) I am familiar with the report entitled: Cognos Plus Study #11, THE ANTIDEPRESSANT MARKET THROUGH 2014-FOCUS ON EMERGING THERAPIES AND NEW INDICATIONS; Anathea B. Waitekus, et al., Pharmacor, June 23, 2005 (attached herein as exhibit I). Page 6 of the report explains how compositions combining an NK1 antagonist with an antidepressant is of significant interest to thought leaders because recent development activity surrounding this drug shows that this class of agents, once thought to lack potential in the antidepressant market, does indeed possess competitive potential as antidepressants. Accordingly, a combination drug of an NK1

receptor and a selective serotonin reuptake inhibitor (SSRI) is currently in development for the treatment of depression and anxiety. Physician confidence in the efficacy of this combination, and the anticipated favorable tolerability profile of the addition of the substance P antagonists, indicates that the NK1/SSRI combination pill will offer a clinically differentiated option in the crowded antidepressant market when it launches in 2011, as a result garnering peak-year sales within the $1-2 billion range.

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Date: Dec 5, 2005

Stafford McLean

Exhibit I

Cognos Plus Study #11

THE ANTIDEPRESSANT MARKET THROUGH 2014—FOCUS ON EMERGING THERAPIES AND NEW INDICATIONS

June 2005

Cognos Plus
A Pharmacor Service

Decision Resources, Inc.
260 Charles Street
Waltham, Massachusetts 02453
Telephone 781.296.2500 • Telefax 781.296.2550

Table of Contents

market in 2011, shortly after GSK launches NS-2359, and reach almost $4 billion in sales in 2014.

- Although the SNRIs are a well-established class of antidepressants, the development of these agents for new indications is of significant interest to thought leaders. Wyeth's SNRI desvenlafaxine is an antidepressant that will achieve blockbuster status by gaining approval for a new indication. Desvenlafaxine is in development for the treatment of depression and vasomotor symptoms associated with menopause (hot flashes); we expect it to be the first antidepressant approved for both these indications and to garner peak-year sales of close to $3 billion.
- GSK's combination NK1 antagonist is of significant interest to thought leaders because recent development activity surrounding this drug shows that this class of agents, once thought to lack potential in the antidepressant market, does indeed possess competitive potential as antidepressants. GSK is developing a combination therapy of vestipitant, an NK1 receptor antagonist (also known as substance P antagonists), and paroxetine, an SSRI, for the treatment of depression and anxiety. Physician confidence in the efficacy of paroxetine, and the anticipated favorable tolerability profile of the addition of the substance P antagonists, indicates that the vestipitant/paroxetine combination pill will offer a clinically differentiated option in the crowded antidepressant market when it launches in 2011, as a result garnering peak-year sales within the $1-2 billion range.
- Johnson & Johnson's dapoxetine, a well-tolerated SSRI, is waiting approval in the United States for treatment of premature ejaculation. Use of dapoxetine, estimated to launch in 2007, for this indication is of interest to many physicians interviewed by Decision Resources because many of them already prescribe antidepressants, such as the SSRIs, off-label for premature ejaculation: approximately one-quarter of physicians interviewed, including many PCPs, have prescribed antidepressants for this disorder. As the first antidepressant approved for premature ejaculation, dapoxetine will have an advantage in the antidepressant market and as a result will garner $500 million to $1 billion in peak-year sales.
- The development of GSK's radafaxine, a dopaminergic and noradrenergic (DA/N) agent, is notable because this drug's entrance into the market will expand the options available to physicians within the DA/N class, where currently options are limited to bupropion (GSK's Wellbutrin) and, in a few countries, reboxetine (Pfizer's Edronax). Radafaxine, estimated to first launch in 2009, will also enter the European market, where there is a void of DA/N agents approved to treat depression. We anticipate rapid uptake of radafaxine in both the United States and Europe, with the agent garnering more than $1 billion in peak-year sales.

RELATED PROCEEDINGS APPENDIX

(None)

Patent Application
Attorney Docket No. PC10408A

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